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10/763,362	01/23/2004	Mark William Bodmer	674525-2008	7568

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,362	BODMER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *6,10-15,17,25-28,30,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-9, 16, 18-24, 29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/27/04; 1/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-33 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-6, 17-24 and 31 (now claims 1-5, 7-9, 16-24, 29 and 31) drawn to a conjugate comprising a first sequence and a second sequence, (1) wherein the first sequence comprises MHC Class II binding domain of a superantigen, as recited in claim 21, (2) wherein the second sequence is a Notch ligand or fragment, as recited in claim 7, and (3) wherein the second sequence upregulates Notch signaling, as recited in claim 9, filed 5/25/06, is acknowledged. The traversal is on the grounds that the inventions are not independent or distinct, nor would there be an undue burden in searching and examining the pending claims in one application. Enforcing the present restriction requirement would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO, as well as extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional applications filed). Restriction has not been shown to be proper, especially since the requisite showing of serious burden has not been made in the Office Action and there are relationships between the claimed combinations. It is noted that claims 1-5 link inventions 1-1280 and that, upon allowance of claims 1-5, the restriction between groups 1-1280 will be withdrawn. It is further noted that groups 1281-1600 and groups 2561-2880 are method claims depending from the elected product claims. Applicants request rejoinder under the provisions of MPEP § 821.04 of these groups upon allowance of the product claims.

The request for rejoinder of method claims upon allowance of the elected product claims is acknowledged. However, no product is found to be allowable at this time.

As noted above, Applicants do not provide any explanation why the claimed conjugates do not differ in structure and in function. Therefore, the restriction is maintained. The restriction requirement is still deemed proper and is therefore made FINAL.

3. Claims 6, 10-15, 25-28, 30, 32 and 33 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-5, 7-9, 16-24, 29 and 31, drawn to a conjugate comprising a first sequence and a second sequence, (1) wherein the first sequence comprises MHC Class 11 binding domain of a

superantigen, as recited in claim 21, (2) wherein the second sequence is a Notch ligand or fragment, as recited in claim 7, and (3) wherein the second sequence upregulates Notch signaling, as recited in claim 9, are being acted upon in this Office Action.

5. Claims 1, 3, 4-5, 7-9, and 16 are objected to for reciting non-elected embodiments.

6. The disclosure is objected to because of the following informalities: (1) incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 48, line 9 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database, and (2) SEQ ID NO is required at page 66, 67, 68, 69, 70, and Brief description of Drawings for Figure 7, 9, 10 and 11 at page 38.

7. The claims in this application do not commence on a separate sheet or electronic page in accordance with 37 CFR 1.52(b)(3). Appropriate correction is required in response to this action.

8. The listing of references in the specification (pages 78-80) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-5, 7-9, 16-24, 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed conjugate or fusion protein would function as claimed, such as inhibiting or activating any T cell Notch signaling pathways.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

The claims encompass (1) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (2) any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (3) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein for activation of any T cell costimulatory molecule, (4) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein for Notch signaling transduction, (5) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any Notch ligand, or any second sequence derived from any Delta or any Serrate, (6) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein that upregulates expression of any Notch, any protein that upregulates any activity of any Notch, any protein that upregulates any

Notch signaling pathway, (7) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to any antigen presenting cell (APC) surface molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (8) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to antigen presenting cell (APC) surface MHC class II molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, and (9) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to any antigen presenting cell (APC) surface molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway wherein the first sequence is any superantigen, any derivative thereof, any bacterial superantigen, any derivative of any bacterial superantigen, any viral superantigen, any derivative of any viral superantigen, any first sequence "comprises" the MHC class II binding domain of any superantigen, any superantigen is a staphylococcal enterotoxin (SE) selected from the group consisting of SEA, SEB, SEC, SEE, and SHE, Toxic Shock syndrome toxins (TSST-1), Streptococcal enterotoxin (SPE) selected from the group consisting of SPEA, SPEC, and SSA for activating or inhibiting any T cell signaling pathways in treating any diseases.

The only disclosed use of any conjugate mentioned above is for modulating, i.e., inhibiting or stimulating any T cell signaling pathways, upregulating expression of any Notch, upregulating any activity of any Notch signaling pathway, upregulating expression of any Notch ligand, upregulating any activity of any Notch ligand or and downstream component of any Notch signaling pathway for treating any diseases (see specification pages 30-34).

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch. However, none of the conjugate or fusion protein has been demonstrate to have any biological activity. There is a lack of in vivo working examples demonstrating that any conjugate or fusion protein mentioned above when binds to MHC class II molecule expressed on APC and any Notch receptor on T cells upregulates which Notch receptor

expression, or upregulates which activity of which Notch receptor, or affecting which downstream component of Notch signaling pathway. Let alone treating any diseases.

Enablement is not commensurate with how to make and use any conjugate or fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway. This is because "a first sequence comprising a protein" and "second sequence comprising a protein" without the amino acid sequence has no structure, much less function. Further, the term "modulates" encompasses activating and inhibiting T cell signaling pathway, which are mutually exclusive. The specification as filed does not teach which "second sequence" from which protein activates which T cell signaling pathways or T cell receptor signaling transduction, which second sequence from which protein inhibits which T cell signaling pathways or T cell receptor signaling transduction. The specification does not teach how to make and use any Notch ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be substituted, deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway.

With regard to Notch ligand "analog" thereof, the term "analog" encompasses any agent that activates any T cell signaling pathway, any Notch signaling pathway, any downstream events of any Notch signaling in any T cells. It is well known in the art that molecules having highly diverse structural biochemical properties can function as an analog. However, Huang et al (Pharmacol. Therapeutics 86: 201-205, 2000; PTO 892) reviews the daunting task faced by the skilled artisan in developing molecular regulators of protein-protein interactions and notes that the process required long periods of trial and error testing before such suitable compounds could be developed (see page 202, Introduction, in particular). Thus the structure of such analog cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

With regard to "sequence derived from Delta or Serrate", there is insufficient guidance as to the structure of "sequence derived from Delta or Serrate", let alone such sequence is effective for inhibiting which T cell signaling pathways or which downstream component of which Notch

signaling pathways. Likewise, there is also insufficient guidance as structure of sequence derived from Delta or Serrate that is effective for stimulating which T cell signaling pathways or which downstream component of which Notch signaling pathways. This is because the amino acid sequence of such Delta or Serrate sequence is required for the claimed conjugate or fusion protein.

With regard to "first sequence is a protein which binds to APC surface molecule", given the unlimited number of sequence, it is unpredictable which sequence binds to which cell surface molecule on which APC, dendritic cells, macrophage, B cells etc. Likewise, there is insufficient guidance as to which amino acid sequence of which protein from any and all superantigens of bacterial or viral antigen binds to MHC class II surface molecule on APC.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1-5, 7-9, 16-24, 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (2) any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (3) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein for activation of any T cell costimulatory molecule, (4) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein for Notch signaling transduction, (5) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any Notch ligand, or any second sequence derived from any Delta or any Serrate, (6) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second

sequence is any protein that upregulates expression of any Notch, any protein that upregulates any activity of any Notch, any protein that upregulates any Notch signaling pathway, (7) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to any antigen presenting cell (APC) surface molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (8) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to antigen presenting cell (APC) surface MHC class II molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, and (9) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to any antigen presenting cell (APC) surface molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway wherein the first sequence is any superantigen, any derivative thereof, any bacterial superantigen, any derivative of any bacterial superantigen, any viral superantigen, any derivative of any viral superantigen, any first sequence "comprises" the MHC class II binding domain of any superantigen, any superantigen is a staphylococcal enterotoxin (SE) selected from the group consisting of SEA, SEB, SEC, SEE, and SHE, Toxic Shock syndrome toxins (TSST-1), Streptococcal enterotoxin (SPE) selected from the group consisting of SPEA, SPEC, and SSA for activating or inhibiting any T cell signaling pathways in treating any diseases.

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch.

With the exception of the specific fusion or conjugate mentioned above, there is insufficient written description about the structure associated with function of any and all protein in "a first sequence" and a "second sequence" in all the claimed conjugates. This is because a "protein" without the amino acid without the amino acid sequence has no structure, much less function.

With regard to "Notch ligand fragment and analog thereof", the specification as filed does not appear to provide adequate written description support for "analog" and "fragment" of any Notch ligand in the claimed conjugate or fusion protein. The term "analog" encompasses any

agent that activates any T cell signaling pathway, any Notch signaling pathway, any downstream events of any Notch signaling events in any T cells. It is well known in the art that molecules having highly diverse structural biochemical properties can function as an analog. However, the amino acids within the full-length sequence of which Notch ligand such as Delta, or Serra to be substituted, deleted, added and/or combination thereof has not been adequately described. Thus the structure of such fragment and analog of Notch ligand cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

With regard to "sequence derived from Delta or Serrate", there is inadequate written description about the structure of "sequence derived from Delta or Serrate" is effective for inhibiting which T cell signaling pathways or which downstream component of which Notch signaling pathways. There is also insufficient written description about the sequence derived from Delta or Serrate that is effective for stimulating which T cell signaling pathways or which downstream component of which Notch signaling pathways. Without the amino acid sequence, the structure of such "sequence derived from Delta or Serrate" in the claimed conjugate or fusion protein cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

With regard to "first sequence is a protein which binds to APC surface molecule", given the unlimited number of sequence or protein, there is inadequate written description about the structure, i.e. amino acid sequence of such protein, let alone such protein binds to any APC surface molecule, such as MHC class II. The same reasoning applies to any and all superantigens of bacterial or viral antigen that binds to MHC class II surface molecule on APC.

The specification discloses only one conjugate, of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of conjugate or fusion protein to describe the genus for the claimed conjugate. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claim 8 is are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "sequence derived from **Delta**" in claim 8 is indefinite and ambiguous because there are many other proteins are known as delta, i.e. Delta protein from TNF receptor or from T cell receptor. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-4, 16-20, 22-24, 29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat 5,716,623 (issued Feb 10, 1998; PTO 892).

The '623 patent teaches a conjugate comprising a first amino acid sequence of HVS14 protein that binds to Class II major Histocompatibility complex antigen (MHC class II) expressed on antigen presenting cell (APC) such as mononuclear phagocytes, Langerhans dendritic cells and follicular dendritic cell and B cells wherein the HVS14 is linked to a second amino acid comprising an immunoglobulin Fc region (see abstract, col. 5, lines 28-41, col. 6, lines 22-50, col. 7, lines 14-28, in particular) or with the extracellular domain of T lymphocyte antigen CD8 (see col. 15, lines 2-4, in particular). The reference conjugate can be made in the form of a fusion protein (see col. 6, lines 33-57, in particular). The reference conjugate is capable of modulates T cell signaling pathway by activating CD4+ T cells to secrete lymphokines such as interleukin 2 and interferon-γ (see col. 5, line 34-41, in particular). The reference second sequence CD8 is a protein for activation of T cell costimulatory molecule. The reference HVS14 protein is a superantigen derived from virus (see abstract, in particular). The '623 patent also teaches other superantigen from bacteria such as TSST-1, SPE-A, SPE-C, Staphylococcal enterotoxins (SE)

(see col. 5, lines 1-7, in particular). The reference fusion protein is made by expressing the reference fusion protein in host cell (see paragraph 54, Host cell, in particular). The '623 patent also teaches a pharmaceutical composition comprising the reference fusion protein and a physiologically acceptable carriers, excipients or diluents (see Summary of invention, paragraph 69, Administration of HVS14 Protein Compositions, in particular). Thus, the reference teachings anticipate the claimed invention.

16. Claims 1-4, 16-20, 22-24, 29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/26747 publication (June 25, 1998; PTO 1449).

The WO 98/26747 publication a conjugate comprising a tumor specific antigen such as MAGE-1, MAGE3, MART-1 conjugated to or fused to a second sequence comprises a protein such as superantigen TSST-1 or SEB that activates T cell signaling pathway by stimulating anti-tumor effects or proliferation of CD4+ T cells (see claims 20-22 of WO 98/26747 publication, pages 10, page 22, in particular). The reference conjugate can be created as a fusion protein (see page 34, Example 2, in particular). The reference tumor antigen in the conjugate or fusion protein binds to an antigen surface molecule such as MHC class II molecule expressed on antigen presenting cells (see page 9, in particular). The reference supperantigens such as SEA, SEB, SEC, SED, SEE, TSST-1, SPE-A, SPE-B, SPE-C are derived from bacteria (see page 35, in particular). The reference fusion protein is made by culturing host cell expressing the reference fusion protein (see abstract, claim 31 of the publication, in particular). The publication also teaches a pharmaceutical composition comprising the reference conjugate or fusion protein and pharmaceutical acceptable carrier such as buffered saline, (see claim 22 of the 'publication, page 36, 3rd paragraph, page 17, Pharmaceutical compositions and Their Preparation, in particular). Thus, the reference teachings anticipate the claimed invention.

17. Claims 1-2, 5, 7-9, 19 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 6,004,924 (issued Dec 21, 1999; PTO 892) as evidence by Hoyne et al (International Immunology 12(2): 177-185, Feb 2000; PTO 892).

The '924 patent teaches a fusion protein comprising a first sequence such as notch fused to a second sequence such as Serrate from human, chicken or Drosphila, which is a Notch ligand that promotes the Serrate function (agonist of Notch) (see col. 23, lines 19-21, col. 24, line 47, col. 25, lines 12-17, col. 50, lines 39-48, col. 51, lines 21-23, in particular). Because Serrate is a

ligand for Notch receptor, it's binding to Notch inherently upregulates its function or activity of Notch (see col. 24, line 48, col. 16, lines 39-47, in particular). The '924 patent further teaches various Notch ligand such as Delta (see col. 4, lines 33-35, Fig. 13, in particular). The reference fusion protein is useful for treating malignancy (see col. 25, lines 49-29, col. 27, line 45, in particular). As evidence by the teachings of Hoyne et al, Serrate 1 (also known as Jagged 1), a ligand for Notch receptor expressed on APC while the receptor Notch is expressed on CD4+ T cells modulates, i.e. decreases T cell signaling such as IL-2 and IFNγ production (see abstract, page 182, col. 2 For Notch signaling, in particular). The reference conjugate is made by culturing host cell expressing the reference protein (see paragraph 20-39, in particular). The '924 patent further teaches a pharmaceutical composition comprising the reference fusion protein and a carrier such as a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered (see paragraph 184, in particular). A product is a product, irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

18. Claims 1-4, 16-20, 22-24, 29 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,340,461 B1 (filed Dec 17, 1997; PTO 892).

The '461 patent teaches a conjugate comprising a first sequence such as tumor specific antigen MAGE-1, MAGE3, MART-1 conjugated to or fused to a second sequence comprises a protein such as superantigen TSST-1 or SEB that activates T cell signaling pathway such as stimulates anti-tumor effects proliferation of CD4+ T cells (see claims of '461, col. 30, lines 21-26, col. 25, lines 23-26, in particular). The reference conjugate can be created as a fusion protein (see col. 30, line 22-26, in particular). The reference tumor antigen in the conjugate binds to an antigen surface molecule such as MHC class II molecule expressed on antigen presenting cells (see col. 17, lines 50-53, in particular). The reference supperantigens such as SEA, SEQB, SEC, SED, SEE and TSST-1 are derived from bacteria Staphylococcus aureus while SPE-A, SPE-C are derived form bacteria Streptococcus pyrogenes (see col. 6, lines 15-33, in particular). The '461 patent teaches the reference fusion protein is made by culturing host cell expressing the reference fusion protein (see Summary of invention, in particular). The '461 patent further teaches a pharmaceutical composition comprising the reference fusion protein and a carrier (see Summary of invention, in particular). Thus, the reference teachings anticipate the claimed invention.

19. Claims 1-4, 16-24, 19 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat 6,514,498 B1 (filed Aug 12, 1996; PTO 892).

The '498 patent teaches a conjugate comprising a first sequence comprising the MHC class II binding domain of the superantigen SEE conjugated to or linked to a second sequence comprises a protein such as IL-2, which stimulates T cell signaling pathway such as T cell proliferation. The reference conjugate can be created as a fusion protein (see col. 7, line 19-20, in particular). The reference MHC class II binding domain inherently binds to MHC class II molecule expressed on antigen presenting cells. The '498 patent also teaches other supperantigens such as TSST-1, SEB, SEC1, SE3, SEC2, SEA, SED and they are derived from bacteria Staphylococcus (see Figure 2, Fig 6, paragraph bridging col. 2 and 3, in particular). The '498 patent teaches the reference conjugate is made by culturing host cell expressing the reference conjugate (see paragraph 23, in particular). The '498 patent further teaches a pharmaceutical composition comprising the reference fusion protein and a carrier such as PBS (see paragraph 24, in particular). Thus, the reference teachings anticipate the claimed invention.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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